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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOSITIONS AND METHODS FOR REGULATION OF TUMOR NECROSIS FACTOR-ALPHA

(57) Abstract: The present invention relates to compositions and methods relating to an interleukin18- inducible cytokine termed tumor necrosis factor-alpha inducing factor (TAIF) or interleukin-32 (IL-32). In particular, the present invention provides compositions and methods for treating autoimmune diseases and cancer, in part by regulation of tumor necrosis factor-alpha expression.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/37578

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **C07K 16/00**(2006.01),**19/00**(2006.01);**A61K 39/00**(2006.01);**C07H 21/00**(2006.01)

USPC: 530/351;514/2;536/23.5
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 530/351; 514/2; 536/23.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
GenEmbl, Geneseq, Patents, PGPub, EST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO02059260 (Tang, et al) 01 August 2002 see SEQ ID NO. 118, especially pages 20-22, 26-29	1,5, 6, 8-10
A	DIAS, et al. Shotgun sequencing of the human transcriptome with ORF expressed sequence tags Proc. Natl. Acad. Sci. 2000, Vol. 97. No. 7, pages 3491-3496, whole document	1,5, 6, 8-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/37578

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1,5,6 and 8-10

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1, 5, 6, 8-10, drawn to a purified nucleic acid of SEQ ID NO: 15.

Group II, claim(s) 2 and 7, drawn to a nucleic acid encoding an amino acid sequence of SEQ ID NO: 7.

Group III, claim(s) 3 and 7, drawn to a nucleic acid encoding an amino acid sequence of SEQ ID NO: 8.

Group IV, claim(s) 4, drawn to a nucleic acid encoding an amino acid sequence of SEQ ID NO: 10.

Group V, claim(s) 7, drawn to a nucleic acid of SEQ ID NO: 6.

Group VI, claim(s) 11,15-18, drawn to a protein encoded by SEQ ID NO: 15.

Group VII, claim(s) 12, drawn to the protein IL-32, wherein IL-32 is an alpha isoform comprising SEQ ID NO: 7.

Group VIII, claim(s) 13, drawn to the protein IL-32, wherein IL-32 is an beta isoform comprising SEQ ID NO: 8.

Group IX, claim(s) 14, drawn to the protein IL-32, wherein IL-32 is an delta isoform comprising SEQ ID NO: 10.

Group X, claim(s) 19-26, drawn to an antibody that binds the protein of SEQ ID NO: 15.

Groups XI-XIV, claim(s) 27-30, drawn to a method for inducing TNF□ production comprising contacting at least one cell with an IL-32 protein consisting of an alpha, beta, gamma or delta isoform, respectively.

Groups XV-XVIII, claim(s) 31-37, drawn to a method of administering an antibody that binds to IL-32, wherein IL-32 is selected from the group consisting of an alpha, beta, gamma or delta isoform, respectively.

Groups XIX-XXIII, claim(s) 38-41, drawn to a method for screening inhibitors of IL-32, wherein IL-32 is selected from the group consisting of SEQ ID NO: 15, an alpha, beta, gamma or delta isoform, respectively.

Groups XXIV-XXVIII, claim(s) 42-44, drawn to method of administering IL-32 protein, wherein IL-32 is selected from the group consisting of an alpha, beta, gamma or delta isoform, respectively.

The inventions listed as Groups I-XXVIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Claim 1 broadly encompasses any nucleic acid sequences that is at least 80% identical to SEQ ID NO: 15. Gaiger, *et al* (WO0164886) teach a nucleic acid sequence (SEQ ID NO: 571) which has 98.5% homology to the nucleic acid sequence of SEQ ID NO: 15. Thus, the ~~special technical feature of claim 1 is not a contribution over the prior art and is not considered a special technical feature. Groups II-V~~

recites the special technical feature of nucleic acid encoding different isoforms of Il-32. Group VI recites the special technical feature of a protein of SEQ ID NO: 15. Groups VII-IX recite the special technical feature of different isoforms of the Il-32 protein. Group X recites the special technical feature of an antibody that binds to the protein of SEQ ID NO: 15 which is not required by the other groups. Groups XI-XIV recite the special technical feature of a method for inducing TNFa production which is not shared by the other groups. Groups XIX-XXIII recite the special technical feature of a method for screening inhibitors of IL-32 which is not shared by the other groups. Groups XXIV-XXVIII recite the special technical feature of a method of administering IL-32 proteins of various isoforms which is not shared by the other groups.